Smek1/2 is a nuclear chaperone and cofactor for cleaved Wnt receptor Ryk, regulating cortical neurogenesis.

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Authors: Wen-Hsuan Chang, Si Ho Choi, Byoung-San Moon, Mingyang Cai, Jungmook Lyu, Jinlun Bai, Fan Gao, Ibrahim Hajjali, Zhongfang Zhao, Daniel B Campbell, Leslie P Weiner, Wange Lu

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Public Summary:
The receptor-like tyrosine kinase (Ryk), a Wnt receptor, is important for cell fate determination during corticogenesis. During neuronal differentiation, the Ryk intracellular domain (ICD) is cleaved. Cleavage of Ryk and nuclear translocation of Ryk-ICD are required for neuronal differentiation. However, the mechanism of translocation and how it regulates neuronal differentiation remain unclear. Here, we identified Smek1 and Smek2 as Ryk-ICD partners that regulate its nuclear localization and function together with Ryk-ICD in the nucleus through chromatin recruitment and gene transcription regulation. Smek1/2 double knockout mice displayed pronounced defects in the production of cortical neurons, especially interneurons, while the neural stem cell population increased. In addition, both Smek and Ryk-ICD bound to the Dlx1/2 intergenic regulator element and were involved in its transcriptional regulation. These findings demonstrate a mechanism of the Ryk signaling pathway in which Smek1/2 and Ryk-ICD work together to mediate neural cell fate during corticogenesis.

Scientific Abstract:
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